

Application No. 09/859,503

**APPENDIX C**

U.S. Patent No. 5,849,780: front page and columns 17, 18 and 93-100.



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# United States Patent [19]

Di Malta et al.

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[54] 1-BENZENESULFONYL-1,3-DIHYDROINDOL-2-ONE DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT

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## Related U.S. Application Data

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[58] Field of Search ..... 548/411; 514/409; 540/602; 544/62, 144, 373; 546/187, 201, 256, 277.7

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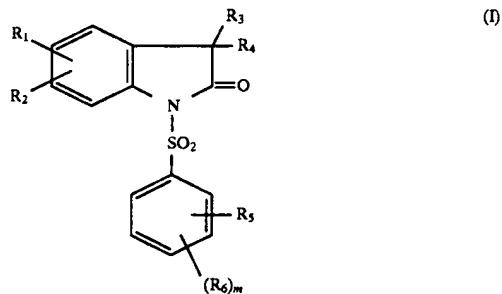
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## ABSTRACT

The invention relates to 1-Benzenesulfonyl-1,3-dihydroindol-2-one derivatives of the formula



and their salts, where appropriate, to their preparation and to pharmaceutical compositions in which they are present. These compounds have an affinity for the vasopressin and/or oxytocin receptors.

31 Claims, No Drawings

prepared from a precursor of formula (I') substituted by a group  $R_1'$ ,  $R_2'$ ,  $R_3'$ , and/or  $R_5'$ , called a precursor group of  $R_1$ ,  $R_2$ ,  $R_3$  and/or  $R_5$ , by using methods known to those skilled in the art.

The description which follows relates to the preparation of the compounds of formula (I) carrying substituents  $R_1$  and/or  $R_5$ ; the same methods apply to the preparation of the compounds in which the substituents  $R_2$  and/or  $R_6$  have the meanings indicated for  $R_1$  and  $R_5$ .

The compounds (I) in which  $R_1$  and/or  $R_5$  are a hydroxyl can be obtained by the catalytic hydrogenation of a compound of formula (I') in which  $R_1'$  and/or  $R_5'$  are a benzyloxy, for example in the presence of palladium-on-charcoal. These compounds can also be prepared from analogous compounds of formula (I') in which  $R_1'$  and/or  $R_5'$  are an amino group by using the method described in J. Org. Chem., 1977, 4, 2053.

The compounds of formula (I) in which  $R_1$  and/or  $R_5$  are a  $C_1$ - $C_7$ -alkoxy can be prepared directly by the process according to the invention starting from the correctly substituted compounds of formulae (II) and (III).

The compounds (I') in which  $R_1'$  and/or  $R_5'$  are a hydroxyl can also be used to prepare compounds (I) in which  $R_1$  and/or  $R_5$  are a  $C_1$ - $C_7$ -alkoxy by reaction with a  $C_1$ - $C_7$ -alkyl halide in the presence of a base such as a metal hydride or an alkali metal or alkaline earth metal carbonate like  $K_2CO_3$  or  $Cs_2CO_3$ , in a solvent such as THF or DMF. Likewise, the compounds of formula (I) in which  $R_1$  and/or  $R_5$  are an  $\omega$ -aminoalkoxy are prepared by reacting an  $\omega$ -chloroalkylamine with the compounds in which  $R_1'$  and/or  $R_5'=\text{OH}$ ; similarly, the compounds in which  $R_1$  and/or  $R_5$  are an  $\omega$ -hydroxyalkoxy are prepared by reaction with a chloroalkyl alcohol; in the particular case of the preparation of a compound (I) in which  $R_1$  and/or  $R_5=\text{O}(\text{CH}_2)_2\text{OH}$ , it is also possible to react ethylene carbonate with a compound (I') in which  $R_1'$  and/or  $R_5'=\text{OH}$ .

The compounds of formula (I) in which  $R_1$  and/or  $R_5$  are a  $C_1$ - $C_7$ -acyloxy which is a  $C_1$ - $C_6$ -alkylcarbonyloxy are obtained by reacting an acid halide or an anhydride with a compound (I') in which  $R_1'$  and/or  $R_5'$  are a hydroxyl.

The compounds of formula (I) in which  $R_1$  and/or  $R_5$  are a formyloxy are obtained for example by reacting formic acid in the presence of dicyclohexylcarbodiimide with a compound (I') in which  $R_1'$  and/or  $R_5'$  are a hydroxyl (J. HUANG et al, J. Chem. Res.(S), 1991, 292-293).

The compounds of formula (I) in which  $R_5$  is a group  $-\text{OR}_7$ ,  $R_7$  being an  $\omega$ -carbamoyl- $C_1$ - $C_7$ -alkyl which is free or substituted by one or two  $C_1$ - $C_7$ -alkyls, can be prepared from a compound (I') in which  $R_5'$  is a group  $-\text{OR}_7$ ,  $R_7$  being an  $\omega$ -carboxy- $C_1$ - $C_7$ -alkyl esterified by a  $C_1$ - $C_7$ -alkyl. This preparation is carried out by reaction with a correctly chosen amine in a manner conventional to those skilled in the art.

To prepare compounds of formula (I) in which  $R_1$  and/or  $R_5$  are a  $C_1$ - $C_7$ -monoalkylamino, a compound of formula (I') in which  $R_1'$  and/or  $R_5'$  are an amino group is reacted with an aldehyde or ketone in an acid medium, in the presence of a reducing agent such as sodium cyanoborohydride; the compounds (I) in which  $R_1$  and/or  $R_5$  are a dialkylamino are prepared by an identical reaction.

The compounds of formula (I) in which  $R_5$  is an amino group substituted by a benzyl, which is itself optionally substituted, or by a  $C_3$ - $C_8$ -alkene in which the double bond may be in the  $C_3$ - $C_4$  position, can be prepared by reacting a benzyl chloride or a  $C_3$ - $C_8$ -chloroalkene with a compound of formula (I') in which  $R_5'$  is an amino or alkylamino group.

The compounds of formula (I) in which  $R_5$  is a  $\Delta 3$ -pyrrolin-1-yl group are prepared by reacting cis-1,4-

dichlorobut-2-ene with the compounds of formula (I') in which  $R_5'$  is an amino group, in the presence of a base such as triethylamine, under an inert atmosphere. The compounds of formula (I) in which  $R_5$  is a pyrrolidin-1-yl group are then prepared by hydrogenation. The reaction of cis-1,4-dichlorobut-2-ene with the compounds (I') in which  $R_5'$  is an amino group can also be carried out in air, in the presence of a base such as sodium carbonate, under which conditions it results in the formation of a mixture of a compound of formula (I) in which  $R_5$  is a  $\Delta 3$ -pyrrolin-1-yl and a compound of formula (I) in which  $R_5$  is a pyrrol-1-yl group, which can be separated by chromatography.

The compounds of formula (I) in which  $R_5$  is an isindolin-2-yl group are prepared by reacting  $\alpha,\alpha'$ -dibromo- $\omega$ -xylene with the compounds of formula (I') in which  $R_5'$  is an amino group, in the presence of a base such as triethylamine, and in a solvent such as dimethylformamide, under reflux.

The compounds of formula (I) in which  $R_5$  is a 1-methyl-2,4-dioxoimidazolin-3-yl group ( $\text{NR}_8\text{R}_9=\text{N-methylhydantoin}$ ) are prepared in two steps: Sarcosine is reacted with a compound of formula (I') in which  $R_5'$  is a phenoxycarbamido, in the presence of a base such as triethylamine, to give a compound of formula (I) in which  $R_5$  is an  $N'$ -carboxymethyl- $N'$ -methylureido; the previously obtained product then cyclizes on heating at 100° C. under vacuum. The compounds of formula (I) in which  $R_5$  is a 2,4-dioxoimidazolin-3-yl group ( $\text{NR}_8\text{R}_9=\text{hydantoin}$ ) are prepared in the same manner by reacting glycine with a compound of formula (I') as defined above.

If  $R_1'$  and/or  $R_5'$  are an amino, it is also possible to perform a nitrosation, for example in the presence of nitrous acid or sodium nitrite, in order to prepare a compound (I') in which  $R_1'$  and/or  $R_5'$  are a diazonium salt; reactions known to those skilled in the art then afford the compounds (I)

according to the invention in which  $R_1$  and/or  $R_5$  are a cyano, a halogeno or a  $\text{C}_1$ - $\text{C}_7$ -alkyl. Finally, compounds (I) in which  $R_1$  and/or  $R_5$  are a group of the formula  $\text{RCONH}-$ ,  $\text{ROCONH}-$ ,  $\text{RNHCONH}-$  or  $\text{RSO}_2\text{NH}-$ , in which R is a  $C_1$ - $C_7$ -alkyl, a phenyl or a benzyl, can be prepared by conventional reactions starting from compounds (I') in which  $R_1'$  and/or  $R_5'=\text{NH}_2$ .

The compounds of formula (I) in which  $R_5$  is a  $C_1$ - $C_7$ -alkoxycarbonyl can be prepared directly by the process according to the invention. Using methods known to those skilled in the art, they make it possible to obtain the compounds of formula (I) in which  $R_5$  is a carboxyl group.

The compounds of formula (I') in which  $R_5'$  is a benzylloxycarbonyl can also be used to obtain the compounds (I) in which  $R_5$  is a carboxyl by catalytic hydrogenation. Reaction with a thionyl halide gives the compounds of formula (II) in which  $R_5$  is a halogenocarbonyl. Such compounds are used to prepare compounds of formula (I) in which  $R_5$  is a carbamoyl substituted by  $R_6'$  and  $R_6''$  by reaction with a compound  $\text{HNR}_6'\text{R}_6''$ . The compounds of formula (I') in which the substituent  $R_5'$  is a phenoxy carbonyl can also be used to obtain the compounds (I) in which  $R_5$  is a phenylcarbamoyl or a  $C_1$ - $C_7$ -alkylcarbamoyl by reaction with an aniline or a  $C_1$ - $C_7$ -alkylamine. An aniline substituted on the phenyl or an alkylamine substituted on the alkyl can be used to obtain compounds of formula (I) in which  $R_5$  is a phenylcarbamoyl substituted on the phenyl or, respectively, an alkylcarbamoyl substituted on the alkyl by  $R_6''$ .

In the same way, the compounds of formula (I) in which  $R_5$  is a group  $-\text{CONHCR}_{10}\text{R}'_{10}\text{COR}_{12}$  are prepared from compounds of formula (I') in which  $R_5'$  is either a group

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DCM is stirred for 2 hours at RT. 40 ml of a saturated solution of  $\text{NaHCO}_3$  are added, the mixture is decanted, the organic phase is washed with water and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using a DCM/MeOH mixture (90/10; v/v) as the eluent to give the expected product.

M.p.=109° C.

#### EXAMPLE 355

5-Ethoxy-1-[4-(N',N'-diethylureido)-2-methoxybenzenesulfonyl]-1,3-dihydro-3-spiro(4-formyloxyhexane)indol-2-one, the More Polar Isomer

A mixture of 0.25 g of the compound obtained in EXAMPLE 343, 0.18 g of cesium carbonate, 0.45 ml of dimethyl sulfate and 12 ml of DMF is heated at 40° C. for 12 hours. 10 ml of water are added, the reaction mixture is extracted with  $\text{AcOEt}$ , the organic phase is washed with water and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using DCM as the eluent to give 0.2 g of the expected product after recrystallization from a cyclohexane/ $\text{AcOEt}$  mixture.

M.p.=155° C.

#### EXAMPLE 356

5-Ethoxy-1-[4-(N',N'-diethylureido)-2-methoxybenzenesulfonyl]-1,3-dihydro-3-spiro(4-acetoxyhexane)indol-2-one, the More Polar Isomer

A mixture of 3 g of the compound obtained in EXAMPLE 343, 0.75 g of 4-dimethylaminopyridine, 3 ml of acetic anhydride and 5 ml of DCM is heated at 40° C. for 5 hours. Water is added to the reaction mixture, extraction is carried out with DCM, the extract is washed with water and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using a DCM/cyclohexane mixture as the eluent to give the expected product after recrystallization from iso ether.

M.p.=140° C.

#### EXAMPLE 357

A) 5-Ethoxy-1,3-dihydro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(8,9-dihydroxytricyclo[5.2.1.0<sup>2,6</sup>]decan-4-yl)indol-2-one  
B) 5-Ethoxy-1,3-dihydro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(8,9-epoxytricyclo[5.2.1.0<sup>2,6</sup>]decan-4-yl)indol-2-one

A mixture of 0.3 g of 5-ethoxy-1,3-dihydro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(tricyclo-[5.2.1.0<sup>2,6</sup>]dec-8-en-4-yl)indol-2-one and 0.2 g of metachloroperbenzoic acid in 20 ml of DCM is stirred for 3 hours at RT. 15 ml of a saturated solution of  $\text{NaHCO}_3$  are added, the mixture is decanted, extraction is carried out with DCM, the extract is dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using DCM as the eluent to give 0.25 g of the expected product after recrystallization from an acetone/DCM mixture.

M.p.=263° C.

B) 5-Ethoxy-1,3-dihydro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(8,9-dihydroxytricyclo[5.2.1.0<sup>2,6</sup>]decan-4-yl)indol-2-one

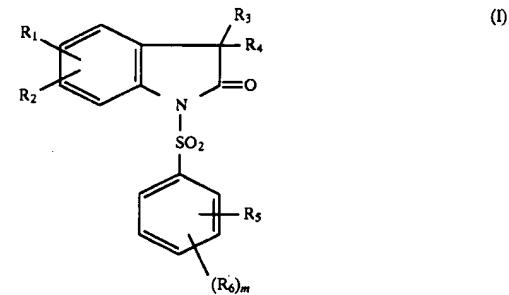
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A mixture of 0.2 g of the compound obtained in the previous step, 20 ml of water, 2 ml of concentrated sulfuric acid and 20 ml of THF is refluxed for 8 hours. The reaction mixture is neutralized by the addition of a saturated solution of  $\text{NaHCO}_3$ , the solvent is evaporated off under vacuum, the residue is extracted with DCM and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using a DCM/MeOH mixture (99/1; v/v) as the eluent to give 0.17 g of the expected product.

M.p.=150° C.

What is claimed is:

1. A compound of formula



in which

$R_1$  and  $R_2$  are each independently a hydrogen, a hydroxy, a  $C_1-C_7-\omega$ -halogenoalkoxy, a halogen, a  $C_1-C_7$ -alkyl, a trifluoromethyl, a  $C_1-C_7$ -alkoxy, a  $C_1-C_7$ -polyhalogenoalkoxy, a  $C_2-C_7-\omega$ -hydroxyalkoxy, an  $\omega$ -methoxyalkoxy in which the alkyl is  $C_2-C_7$ , a  $C_2-C_7-\omega$ -aminoalkoxy which is free or substituted by one or two  $C_1-C_7$ -alkyls; a  $C_3-C_7$ -cycloalkoxy; a cycloalkyl methoxy in which the cycloalkyl is  $C_3-C_7$ ; a phenoxy; a benzoyloxy; a  $C_1-C_7$ -alkylthio; a phenylthio; a nitro; an amino which is free or substituted by one or two  $C_1-C_7$ -alkyls; a cyano; a  $C_1-C_7$ -acyl; a  $C_1-C_7$ -acyloxy; a  $C_1-C_7$ -alkylsulfonamido; a phenylsulfonamido; a benzylsulfonamido; a  $C_1-C_7$ -alkylamido; a  $C_1-C_7$ -alkoxycarbonylamino; a ureido which is unsubstituted or substituted by a phenyl, by a benzyl or by one or two  $C_1-C_7$ -alkyls; or a thioureido which is unsubstituted or substituted by a phenyl, by a benzyl or by one or two  $C_1-C_7$ -alkyls;

$R_3$  and  $R_4$ , together with the carbon to which they are bonded, form an optionally fused, saturated or unsaturated  $C_3-C_{12}$  hydrocarbon ring which is unsubstituted or substituted by one or more  $C_1-C_7$ -alkyl groups, by an oxo group, by a  $C_3-C_5$ -spirocycloalkyl or by a hydroxy which is free or substituted by a group selected from the group consisting of  $C_1-C_4$ -alkyl groups,  $C_1-C_2$ -alkoxyalkyl groups in which the alkyl is  $C_1-C_4$ , phenylalkoxyalkyl groups in which the alkoxy is  $C_1-C_2$  and the alkyl is  $C_1-C_4$ , and tetrahydrofuranyl and tetrahydropyranyl groups; or else

$R_5$  and  $R_6$  are each independently a hydrogen, a halogen, a  $C_1-C_7$ -alkyls, a trifluoromethyl, a cyano, a nitro, an amino which is free or substituted by one or two  $C_1-C_7$ -alkyls; a hydroxyamino; a hydroxy; a carboxy; a guanidino which is unsubstituted or mono-substituted or disubstituted by a  $C_1-C_7$ -alkyl, a phenyl or a benzyl; a group  $OR_7$ ; a group  $SR_7$ ; a  $C_1-C_7$ -acyl; a  $C_1-C_7$ -alkoxycarbonyl; a phenoxy carbonyl; a benzyl oxycarbonyl; a carbamoyl substituted by groups  $R'_6$  and  $R''_6$ ; a thiocarbamoyl which is free or substituted by one or two  $C_1-C_7$ -alkyls; a sulfamoyl; an alkylsulfamoyl or

dialkylsulfamoyl in which the alkyl is  $C_1-C_7$ ; a group  $SO_2R'$ ; an alkylsulfonamido in which the alkyl is  $C_1-C_7$ ; a phenylsulfonamido; a benzylsulfonamido; a group  $COR'$ ; a group  $NR_6R_9$  or a group  $CO-NH-CR_{10}R'_{10}-COR_{12}$ ; the phenyl group forming part of the substituent  $R_5$  and/or  $R_6$  can be unsubstituted or monosubstituted or polysubstituted by a  $C_1-C_7$ -alkyl, a trifluoromethyl, a  $C_1-C_7$ -alkoxy, a halogen, a sulfamoyl, an alkylsulfamoyl in which the alkyl is  $C_1-C_7$ , a carboxy, an alkoxycarbonyl in which the alkyl is  $C_1-C_7$ , a  $C_1-C_7$ -acyloxy or an imidazolyl;  $R_6$  and  $R''_6$  are each independently hydrogen, a  $C_1-C_7$ -alkyl which is unsubstituted or substituted by one or more halogens or by  $R''_6$ ; a phenyl, a pyridyl, a methylpyridyl, a piperidin-4-yl or a methylpiperidin-4-yl; or  $R_{10}$  and  $R''_6$  form, with the nitrogen atom to which they are bonded, a pyrrolidino group which is unsubstituted or substituted by a hydroxymethyl or by a carbamoyl which is free or substituted by one or two  $C_1-C_7$ -alkyls;  $R'''_6$  is a hydroxy, a  $C_1-C_7$ -alkoxy; an amino which is free or substituted by one or two  $C_1-C_7$ -alkyls; a carbamoyl which is free or substituted by one or two  $C_1-C_7$ -alkyls or in which the two substituents, together with the nitrogen atom to which they are bonded, form a pyrrolidino, a piperidino or an azepino; a cyano; a carboxy which is free or esterified by a  $C_1-C_7$ -alkyl or by a benzyl; a phenyl; a  $C_3-C_7$ -cycloalkyl; an adamantyl or a heterocyclic radical selected from pyridyl, methylpyridyl, furanyl, tetrahydrofuran, thienyl, methylthienyl, pyrrolidino, piperidino and azepino groups;  $R_7$  is a  $C_1-C_7$ -alkyl, a phenyl, a benzyl, a  $C_3-C_7$ -cycloalkyl, a  $C_2-C_7$ -alkenyl, a  $C_1-C_7-\omega$ -halogenoalkyl, a  $C_1-C_7$ -polyhalogenoalkyl, a  $C_1-C_7$ -acyl, a  $C_1-C_7-\omega$ -carboxyalkyl which is free or esterified by a  $C_1-C_7$ -alkyl or by a benzyl; a  $C_2-C_7-\omega$ -aminoalkyl in which the amino group is free, substituted by one or two  $C_1-C_7$ -alkyls or in the form of an ammonium ion with a physiologically acceptable anion; or a  $C_1-C_7-\omega$ -carbamoylalkyl which is free or substituted by one or two  $C_1-C_7$ -alkyls;  $R_7$  is a piperazin-1-yl group which is unsubstituted or substituted in the 4-position by a group  $R''_7$ ; a piperidino group which is unsubstituted or substituted in the 4-position by a group  $R'''_7$ ; an azetidin-1-yl group which is unsubstituted or substituted in the 3-position by a group  $R''_7$ ; a pyridyl group which is unsubstituted or substituted by a methyl; or a pyrrolidino group which is substituted by a group  $R''''_7$ ;  $R''_7$  is a  $C_1-C_7$ -alkyl, a phenyl, a benzyl or a  $C_1-C_7$ -acyl;  $R'''_7$  is  $R''_7$ , or an amino which is free or carries a protecting group;  $R''''_7$  is  $R''_7$ , or a carboxy group which is free or esterified by a  $C_1-C_7$ -alkyl;  $R_8$  and  $R_9$  are each independently a hydrogen, a  $C_1-C_7$ -alkyl or a benzyl;  $R_9$  can also be a  $C_3-C_8$ -alkene in which the double bond is in the  $C_3-C_4$ -position; a  $C_1-C_7$ -acyl; a  $C_1-C_7$ -thioacyl; a cycloalkylcarbonyl in which the cycloalkyl is  $C_3-C_7$ ; a cycloalkylthiocarbonyl in which the cycloalkyl is  $C_3-C_7$ ; a  $C_1-C_7-\omega$ -aminoacyl; a  $C_1-C_7-\omega$ -hydroxyacyl; a  $C_1-C_7-\omega$ -benzyl-oxyacyl; a phenoxy carbonyl; a thienocarbonyl a pyridylcarbonyl; a methylpyridylcarbonyl; a  $C_1-C_7$ -alkoxycarbonyl; a benzoyl; a phenacyl; a group  $CO-CR_{10}R'_{10}-NR_{11}R'_{11}$ ; a group  $CR_{10}R'_{10}COR_{12}$ ; a

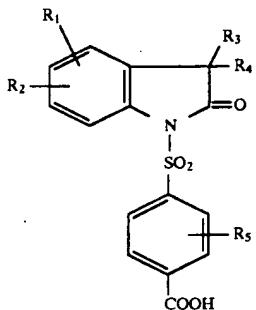
group  $(CH_2)_2COR_{12}$ ; a group  $CO(CH_2)_2COR_{12}$ ; a carbamoyl which is unsubstituted or substituted by  $R_{14}$  and  $R'_{14}$ ; a thiocarbamoyl which is unsubstituted or substituted by  $R_{14}$  and  $R'_{14}$ ; or a heterocyclic radical selected from pyrazolyl, imidazolyl, triazolyl, tetrazolyl, pyridazinyl, pyrimidinyl, pyridyl and thiazolyl groups; or  $R_8$  and  $R_9$ , together with the nitrogen atom to which they are bonded, form hydantoin, N-methylhydantoin or a heterocycle selected from the group consisting of pyrrole, dihydropyrrole, pyrrolidine and isoindole, in which the benzene ring can be unsubstituted or substituted by a halogen, a  $C_1-C_7$ -alkyl, a trifluoromethyl or a methoxy;  $R_{10}$  and  $R'_{10}$  are each independently hydrogen, a  $C_1-C_7$ -alkyl or a benzyl, or  $R_{10}$  and  $R'_{10}$ , together with the carbon atom to which they are bonded, form a  $C_3-C_7$ -cycloalkyl;  $R_{11}$  and  $R'_{11}$  are each independently hydrogen or a  $C_1-C_7$ -alkyl;  $R_{12}$  and a hydroxy, a  $C_1-C_7$ -alkoxy or an amino which is unsubstituted or substituted by one or two  $C_1-C_7$ -alkyls;  $R_{14}$  and  $R'_{14}$  are each independently a  $C_1-C_7$ -alkyl which is unsubstituted or substituted by  $R_{15}$ , a phenyl which is unsubstituted or substituted by  $R'_{15}$ , a  $C_3-C_7$ -cycloalkyl or an adamantyl; or  $R_{14}$  and  $R'_{14}$ , together with the nitrogen atom to which they are bonded, form a heterocycle selected from morpholine, thiomorpholine, piperazine, azetidine, pyrrolidine, piperidine and azepine, said heterocycle being unsubstituted or substituted by one or more methyl groups, by a phenyl or by an amino group which is free or carries a protecting group;  $R_{15}$  is a phenyl, a pyridyl, a hydroxy, a  $C_1-C_7$ -alkoxy, an amino which is free or substituted by one or two  $C_1-C_7$ -alkyls, or a carboxy which is free or esterified by a  $C_1-C_7$ -alkyl;  $R'_{15}$  is a hydroxy or an amino which is free or substituted by one or two  $C_1-C_7$ -alkyls;  $m$  is 1 or, if  $R_6$  is a halogen, a  $C_1-C_7$ -alkyl or a  $C_1-C_7$ -alkoxy,  $m$  can also be 2, 3 or 4, or else  $(R_6)_m$  can be  $m$  substituents having different meanings selected from halogen,  $C_1-C_7$ -alkyl and  $C_1-C_7$ -alkoxy;  $t$  is an integer which can vary from 2 to 5;  $t'$  is an integer which can vary from 1 to 5; and its salts. 2. A compound according to claim 1, wherein  $R_1$  is in the 5-position of the indole and  $R_2$  is hydrogen. 3. A compound according to claim 1, wherein  $R_1$  is a chlorine or fluorine atom or an ethoxy group in the 5-position of the indole and  $R_2$  is hydrogen. 4. A compound according to claim 1, wherein  $R_3$  and  $R_4$ , together with the carbon to which they are bonded, form a  $C_3-C_{12}$ -hydrocarbon ring. 5. A compound according to claim 1, wherein  $R_3$  and  $R_4$ , together with the carbon to which they are bonded, form a cycloheptane, an adamantane, a tricyclo[5.2.1.0<sup>2,6</sup>]dec-8-ene, a bicyclo[2.2.1]heptane, a bicyclo[3.3.1]nonane or a cyclohexane which is unsubstituted or substituted by a  $C_3-C_5$ -spirocycloalkyl or by one or two  $C_1-C_7$ -alkyl groups. 6. A compound according to claim 1, wherein the substituents  $R_5$  and  $R_6$  are respectively in the 2- and 4-positions. 7. A compound according to claim 6, in which  $R_5$  and  $R_6$  are each a methoxy.

8. A compound according to claim 1, in which R<sub>5</sub> in the 2-position is a methoxy and R<sub>6</sub> in the 4-position is C<sub>1</sub>–C<sub>7</sub>-acylamino, a C<sub>1</sub>–C<sub>4</sub>-dialkylureido or an alkoxy carbonylalkylcarbamoyl in which the alkyl groups are C<sub>1</sub>–C<sub>7</sub>.

9. A compound according to claim 1, wherein R<sub>5</sub> is an orthomethoxy group and R<sub>6</sub> in the para-position is a group selected from the group consisting of:

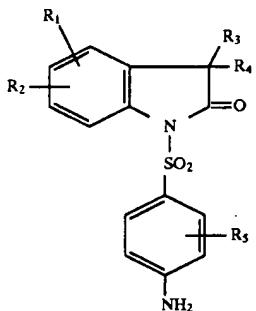
piperidin-1-yl-carbonylamino,  
(2-cyanoprop-2-yl)carbonyl,  
pyrrolidin-1-yl,  
N,N-diethylguanidino and  
N,N-diethylthioureido.

10. A compound according to claim 1, of the formula:



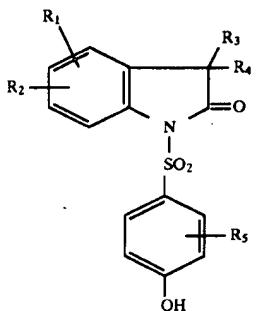
in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are defined as indicated above for (I) in claim 1, and said compound including pharmaceutically acceptable esters of the carboxyl group.

11. A compound according to claim 1, of the formula:



in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are defined as indicated above for (I) in claim 1, and its salts where appropriate.

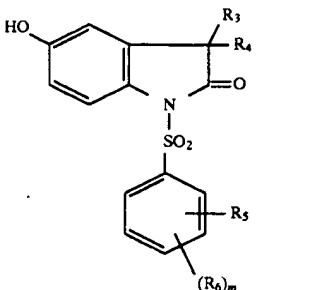
12. A compound according to claim 1, of the formula:



in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are defined as indicated above for (I) in claim 1.

13. A compound according to claim 1, of the formula:

(XII)



15 in which R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and m are defined as indicated above for (I) in claim 1.

14. A pharmaceutical composition which contains a compound according to any one of claims 1 to 13 in combination with a pharmaceutically acceptable carrier or excipient.

20 15. A compound of formula (I) according to claim 1, in which

R<sub>1</sub> and R<sub>2</sub> are each independently a hydrogen, a hydroxyl, a C<sub>1</sub>–C<sub>4</sub>-ω-halogenoalkoxy, a halogen, a C<sub>1</sub>–C<sub>7</sub>-alkyl, a trifluoromethyl, a C<sub>1</sub>–C<sub>7</sub>-alkoxy, a C<sub>1</sub>–C<sub>4</sub>-polyhalogenoalkoxy, a C<sub>2</sub>–C<sub>4</sub>-ω-hydroxyalkoxy, an ω-methoxyalkoxy in which the alkyl is C<sub>2</sub>–C<sub>4</sub>, a C<sub>2</sub>–C<sub>4</sub>-ω-aminoalkoxy which is free or substituted by one or two C<sub>1</sub>–C<sub>4</sub> alkyl groups, a C<sub>3</sub>–C<sub>7</sub>-cycloalkyloxy, a cycloalkylmethoxy in which the cycloalkyl is a C<sub>3</sub>–C<sub>7</sub>, a phenoxy, a benzyloxy, a C<sub>1</sub>–C<sub>4</sub>-alkythio, a phenylthio, a nitro, an amino which is free or substituted by one or two C<sub>1</sub>–C<sub>4</sub>-alkyl groups, a cyano, a C<sub>1</sub>–C<sub>4</sub>-acyl, a C<sub>1</sub>–C<sub>4</sub>-acyloxy, a C<sub>1</sub>–C<sub>4</sub>-alkylsulfonamido, a phenylsulfonamido, a C<sub>1</sub>–C<sub>4</sub>-alkylamido, a C<sub>1</sub>–C<sub>4</sub>-alkoxycarbonylamino, a ureido which is unsubstituted or substituted by a phenyl or by one or two C<sub>1</sub>–C<sub>4</sub>-alkyl groups;

R<sub>3</sub> and R<sub>4</sub> together with the carbon atom to which they are bonded form an optionally fused, saturated or unsaturated C<sub>3</sub>–C<sub>10</sub> hydrocarbon ring, which is unsubstituted or substituted by one or more C<sub>1</sub>–C<sub>7</sub>-alkyl groups or by a C<sub>3</sub>–C<sub>5</sub>-spirocycloalkyl;

or else

R<sub>5</sub> and R<sub>6</sub> are each independently hydrogen, a halogen, a C<sub>1</sub>–C<sub>7</sub>-alkyl, a trifluoromethyl, a cyano, a nitro, an amino which is free or substituted by one or two C<sub>1</sub>–C<sub>7</sub>-alkyl groups, a hydroxy amino, a hydroxy, a carboxy, a group OR<sub>7</sub>, a group SR<sub>7</sub>, a C<sub>1</sub>–C<sub>7</sub>-acyl, a C<sub>1</sub>–C<sub>7</sub>-alkoxycarbonyl, a phenoxy carbonyl, a benzoyloxycarbonyl, a carbamoyl which is substituted by R'<sub>6</sub> and R''<sub>6</sub> groups, a thiocarbamoyl which is free or substituted by one or two C<sub>1</sub>–C<sub>7</sub>-alkyl groups, a sulfamoyl, an alkylsulfamoyl or a dialkylsulfamoyl in which the alkyl is C<sub>1</sub>–C<sub>7</sub>, a SO<sub>2</sub>R'<sub>7</sub> group, an alkylsulfonamido in which the alkyl is C<sub>1</sub>–C<sub>7</sub>, a group COR'<sub>7</sub>, a group NR<sub>8</sub>R<sub>9</sub>, a CO—NH—CH(R<sub>10</sub>)—COR<sub>12</sub> group; the phenyl group forming part of the substituent R<sub>5</sub> and/or R<sub>6</sub> can be unsubstituted or substituted one or more times by a C<sub>1</sub>–C<sub>7</sub>-alkyl, a trifluoromethyl, a methoxy, a halogen, a sulfamoyl, an alkylsulfamoyl in which the alkyl is C<sub>1</sub>–C<sub>7</sub>, a carboxy, a C<sub>1</sub>–C<sub>7</sub>-alkoxycarbonyl, a C<sub>1</sub>–C<sub>7</sub>-acyloxy, an imidazolyl;

R'<sub>6</sub> and R''<sub>6</sub> are each independently hydrogen, a C<sub>1</sub>–C<sub>7</sub>-alkyl which is unsubstituted or substituted by R'''<sub>6</sub>, a phenyl, a pyridyl, a methylpyridyl, a piperidin-4-yl, a methylpiperidin-4-yl, or else R'<sub>6</sub> and R''<sub>6</sub>, together with the nitrogen atom to which they are connected, form a heterocycle selected from piperazine and piperidine;

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$R''_6$  is a hydroxyl, a cyano, a carboxy which is free or esterified by a  $C_1$ - $C_7$ -alkyl or by a benzyl, a phenyl, a pyridyl, a methylpyridyl, an amino which is free or substituted by one or two  $C_1$ - $C_7$ -alkyl groups;

$R_7$  is a  $C_1$ - $C_7$ -alkyl, a phenyl, a benzyl, a  $C_3$ - $C_7$ -cycloalkyl, a  $C_2$ - $C_4$ -alkenyl, a  $C_1$ - $C_7$ - $\omega$ -halogenoalkyl, a  $C_1$ - $C_7$ -polyhalogenoalkyl, a  $C_1$ - $C_7$ -acyl, a  $C_1$ - $C_7$ - $\omega$ -carboxyalkyl which is free or esterified by a  $C_1$ - $C_4$ -alkyl group or by a benzyl, a  $C_2$ - $C_7$ - $\omega$ -aminoalkyl in which the amino group is free or substituted by one or two  $C_1$ - $C_4$ -alkyl groups or in the form of an ammonium ion with a physiologically acceptable anion;

$R'_7$  is a piperazin-1-yl group which is unsubstituted or substituted in the 4-position by a group  $R''_7$ , a piperidino group which is unsubstituted or substituted in the 4-position by a group  $R''_7$ , an azetidin-1-yl group which is unsubstituted or substituted in the 3-position by a group  $R''_7$ , a pyridyl group which is unsubstituted or substituted by a methyl;

$R''_7$  is a  $C_1$ - $C_4$ -alkyl, a phenyl, a benzyl, a  $C_1$ - $C_4$ -acyl;

$R'''_7$  is  $R''_7$ , or an amino which is free or carries a protecting group;

$R_8$  and  $R_9$  are each independently hydrogen, a  $C_1$ - $C_7$ -alkyl, a phenyl, a benzyl;  $R_9$  may also be a  $C_1$ - $C_7$ -acyl, a  $C_3$ - $C_7$ -thialkyl, a cycloalkylcarbonyl in which the cycloalkyl is  $C_3$ - $C_7$ , a cycloalkylthiocarbonyl in which the cycloalkyl is  $C_3$ - $C_7$ , a  $C_1$ - $C_4$ - $\omega$ -aminoacyl, a  $C_1$ - $C_4$ - $\omega$ -hydroxyacyl, a  $C_1$ - $C_4$ - $\omega$ -benzyloxyacyl, a phenoxycarbonyl, a thiencarbonyl, a pyridylcarbonyl, a methylpyridylcarbonyl, a  $C_1$ - $C_4$ -alkoxycarbonyl, a benzoyl, a group  $-\text{CO}-\text{CH}(R_{10})-\text{NR}_{11}\text{R}'_{11}$ , a group  $-\text{CH}(R_{10})-\text{CO}_2\text{R}_{11}$ , a group  $(\text{CH}_2)_n\text{COR}_{12}$ , a group  $\text{CO}(\text{CH}_2)_n\text{COR}_{12}$ , a carbamoyl which is unsubstituted or substituted by a phenyl or by one or two  $C_2$ - $C_4$ -alkyl groups;

$m$  is 1 or, when  $R_6$  is halogen, a  $C_1$ - $C_7$ -alkyl or a  $C_1$ - $C_7$ -alkoxy,  $m$  can also be 2, 3 or 4 or else  $(R_6)_m$  can represent  $m$  substituents having different meanings selected from halogen, a  $C_1$ - $C_7$ -alkyl or a  $C_1$ - $C_7$ -alkoxy;

$R_{10}$  is hydrogen, a  $C_1$ - $C_4$ -alkyl or a benzyl;

$R_{11}$  and  $R'_{11}$  are each independently hydrogen or a  $C_1$ - $C_4$ -alkyl;

$R_{12}$  is a hydroxyl, a  $C_1$ - $C_4$ -alkoxy or an amino which is unsubstituted or substituted by one or two  $C_1$ - $C_4$ -alkyl groups;

$t$  is an integer varying from 1 to 5;

as well as its possible salts.

16. A compound of formula (I) according to claim 15, in which  $R_1$  is chlorine or an ethoxy group in the 5-position of the indole ring and  $R_2$  is hydrogen.

17. A compound of formula (I) according to claim 15, in which  $R_3$  and  $R_4$  together with the carbon atom to which they are bonded form a  $C_3$ - $C_{10}$ -hydrocarbon ring.

18. A compound of formula (I) according to claim 15, in which  $R_3$  and  $R_4$  together with the carbon atom to which they are bonded form a cyclohexane which is unsubstituted or substituted by one or two  $C_1$ - $C_7$ -alkyl groups or by a  $C_3$ - $C_5$ -spirocycloalkyl; a cycloheptane, an adamantane or a tricyclo[5.2.1.0<sup>2,5</sup>]dec-8-ene.

19. A compound of formula (I) according to claim 15, in which  $R_5$  and  $R_6$  are each a methoxy.

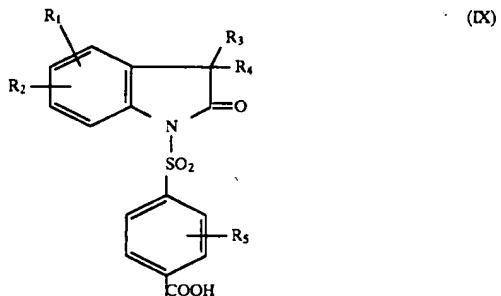
20. A compound of formula (I) according to claim 15, in which  $R_5$  in the 2-position is a methoxy group and  $R_6$  in the

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4-position is a  $C_1$ - $C_7$ -acylamino, a  $C_1$ - $C_4$ -dialkylureido, an alkoxy carbonylalkylcarbamoyl in which the alkyl groups are  $C_1$ - $C_7$ .

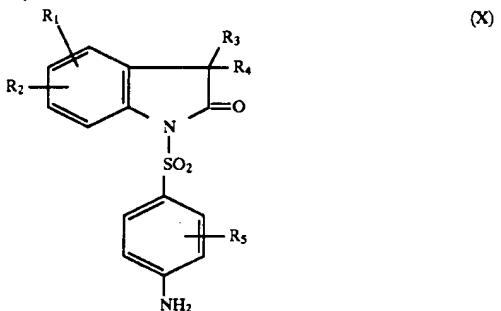
21. A compound of formula (I) according to claim 15, in which  $R_1$  is in the 5-position and  $R_2$  is hydrogen.

22. A compound according to claim 15 of formula:



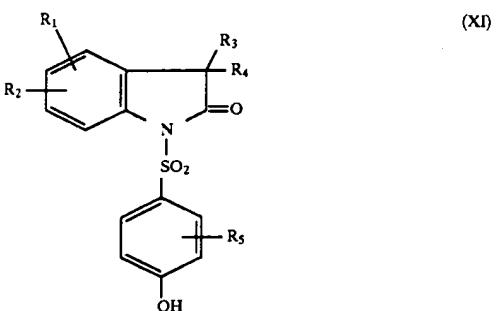
in which  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  are defined as indicated above for (I) in claim 15 and its functional derivatives.

23. A compound according to claim 15, of formula:



in which  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  are defined as indicated above for (I) in claim 15, and its possible salts.

24. A compound according to claim 15 of formula:



in which  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  are defined as indicated above for (I) in claim 15.